SUPPORT FOR THE AMENDMENTS

Claims 2-10, 20, 21, 27-29, 31, 33, 34, 43, and 49 were previously canceled.

Claims 1, 11-19, 22-26, 29, 30, 32-38, and 44-48 are canceled herein.

Claim 39 has been amended.

Claims 50-56 have been added.

The amendment to Claim 39 and the introduction of Claims 50-56 are supported by original Claims 22-29 and the specification as filed, for example, at pages 16-18, page 21, and the Examples.

No new matter has been added by the present amendment.

REMARKS

Claims 39-42 and 50-56 are pending in the present application.

The rejection of Claims 1, 11-15, 30, 32, 35-42, and 44-48 under 35 U.S.C. §103(a) over Nihei et al with Hori et al in view of Fex et al and Sugawara et al are is respectfully traversed.

In the Office Action mailed September 11, 2007, the Examiner has maintained that the claims are obvious over the combined disclosures of Nihei et al, Hori et al, Fex et al, and Sugawara et al. With respect to the product claims, the Examiner cites Sugawara et al as disclosing betamethasone which the Examiner alleges would be obvious to combine with Fex et al to arrive at a composition with betamethasone in combination with AC7700. As for the method claims (i.e., Claims 39-42 and 44-48), the Examiner maintains the rejection in part due to the alleged lack of evidence of unexpected results.

Applicants make no statement with respect to the propriety of the Examiner's allegations set forth in the Office Action mailed September 11, 2007 and in no way acquiesce to the same. Applicants have amended the claims to limit the scope thereof to a method for treatment of tumors, which comprises administering to a subject in need thereof a composition comprising (a) an effective amount of an anti-inflammatory active substance, wherein the anti-inflammatory active substance is a Dexamethasone selected from the group consisting Dexamethasone, an ester of Dexamethasone, and a salt of Dexamethasone; and (b) a tubulin polymerization-inhibitory active substance having anti-tumor activity selected from the group consisting of (Z)-N-[2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)vinyl]phenyl]-L-serinamide and a salt thereof (see Claim 39).

Applicants submit that this invention is not obvious over Nihei et al with Hori et al in view of Fex et al and Sugawara et al. In that Office Action mailed March 13, 2007, the Examiner alleged that the invention was anticipated by Nihei et al, obvious over Hori et al in view of Nihei et al, and obvious over Hori et al taken with Fex et al in view of Nihei et al. Applicants further submit that this invention is not obvious as the Examiner alleged in the Office Action mailed March 13, 2007.

As discussed on pages 1-3 of the specification, tubulin polymerization-inhibitory active substances (e.g., (Z)-N-[2-methoxy-5-[2-(3,4,5-trimethoxyphenyl)vinyl]phenyl]-L-serinamide ("AC-7700") have a relatively narrow safety zone between lethal dose and effective dose. Therefore, there are practical and very real limitations on the medicinal use of AC-7700. For the first time, the present Applicants have shown that the safety zone of AC-7700 can be expanded while maintaining anti-tumor effect. To this end, Applicants discovered that the specific combination of the anti-inflammatory active substance "Dexamethasone" reduced the toxicity of AC-7700.

The Examiner is reminded that as set forth in MPEP §716.02(a) "greater than expected results are evidence of nonobviousness." Evidence of a greater than expected result may also be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (i.e., demonstrating "synergism"). *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989).

In the present case, Applicants have demonstrated in Figures 1 and 2 (see section (6)(1) on page 24) the reduction of AC-7700 toxicity with Dexamethasone. For the Examiner's convenience, Figures 1 and 2 are reproduced below:

Fig.1

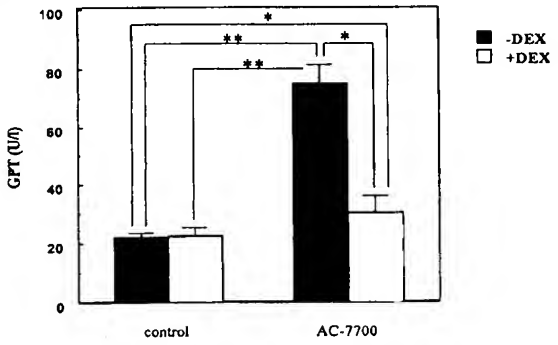


Fig.2

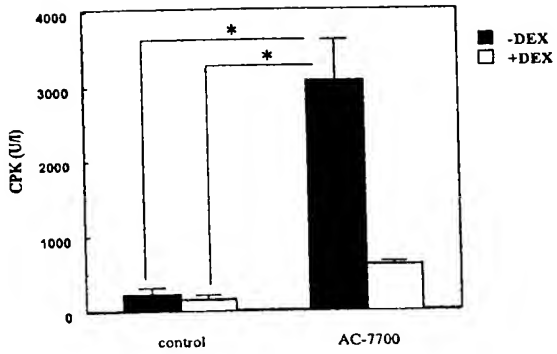


Figure 1 shows results from the toxicity test with tumor-bearing rats from Example 1 (Scheffe's F test; *p<0.05, **p<0.01) F344 rats subcutaneously transplanted MT-9 tumor / Dexamethasone (1mg/kg)/AC-7700 (10mg/kg); Blood biochemical indices: GPT; ■: - DEX; □: + DEX. Figure 2 shows results from the toxicity test with tumor-bearing rats in Example 1 (Scheffe's F test; *p<0.05). F344 rats subcutaneously transplanted MT-9 tumor / Dexamethasone (1mg/kg)/AC-7700 (10mg/kg); Blood biochemical indices: CPK; ■ : - DEX; □ : + DEX.

The results reveal that Dexamethasone had remarkably reduced the toxicity of AC-7700 (10mg/kg), hepatic toxicity (GPT) and cardiovascular toxicity (CPK) in tumor bearing rats. Concerning the gastrointestinal toxicity, the combined use of Dexamethasone with AC-7700 has revealed that diarrhea induced by AC-7700 in mice was significantly improved. The toxicity was unexpectedly and significantly improved.

However, if the combination significantly reduces the pharmaceutical effect on anti-tumor simultaneously (reduction of toxicity), it is meaningless and worthless because the safety zone of AC-7700 is not expanded. Applicants discovered that even if both the AC-

7700 and Dexamethasone were administered, there was no significant deference in the pharmaceutical effect between AC-7700 alone and combination of AC-7700 and Dexamethasone as shown in Table 1 (below).

[Table 1] Influence of Dexamethasone on the pharmaceutical effect of AC-7700

DEX(mg/kg/day)	AC-7700(mg/kg/day)	I.R.(%)
0	0	0
0	10	84**
1	0	21
1	10	72**

(Note: Mann-Whitney's U test; **: $p<0.01$ vs. Control)

Nihei et al disclose that "AC-7700 (a) maintained activity against solid tumor growth when combined with Dexamethasone", but this means only latter part. The combination of AC-7700 and Dexamethasone improves safety zone of AC-7700 significantly, so at least such a combination is very worthy and valuable in practical use of AC-7700. Such effects of the combination are not disclosed and not suggested in the prior arts and advantageous effects are unpredictable.

Applicants submit that at the time that this application was filed, it was unknown that a combination tublin polymerization inhibitory active agent (AC-7700) and anti-inflammatory active substance (Dexamethasone) expands the narrow safety zone of tublin polymerization inhibitory active agent. Thus, Applicants submit that the present invention would not be obvious.

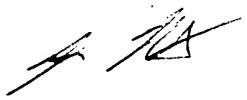
Withdrawal of these grounds of rejection is requested.

Applicants submit that the present application is now in condition for allowance.

Early notice to this effect is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



Stephen G. Baxter
Attorney of Record
Registration No. 32,884

Vincent K. Shier, Ph.D.
Registration No. 50,552

Customer Number
22850

Tel: (703) 413-3000
Fax: (703) 413-2220
(OSMMN 08/03)